

DOCKET NO.: JANS-0026 (JAB-1499 US)

PATENT

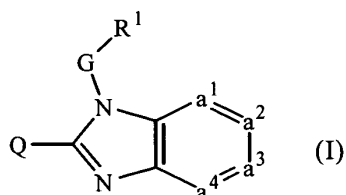
Application No.: 10/019,380

Office Action Dated: October 29, 2003

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. *(previously presented)* A compound of formula

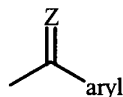


a prodrug, addition salt, or stereochemically isomeric form thereof wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

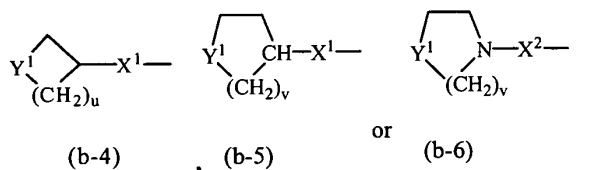


wherein each hydrogen atom in the radical (a-1) may optionally be replaced by halo, C_{1-6} alkyl, nitro, amino, hydroxy, C_{1-6} alkyloxy, polyhalo C_{1-6} alkyl, carboxyl, amino C_{1-6} alkyl, mono- or di(C_{1-4} alkyl)amino C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, hydroxy C_{1-6} alkyl, or a radical of formula



wherein Z is O, $\text{CH}-\text{C}(=\text{O})-\text{NR}^{5a}\text{R}^{5b}$, CH_2 , $\text{CH}-\text{C}_{1-6}\text{alkyl}$, N-OH or N-O- $\text{C}_{1-6}\text{alkyl}$;

Q is a radical of formula



wherein;

Y^1 is a bivalent radical of formula $-\text{NR}^2-$ or $-\text{CH}(\text{NR}^2\text{R}^4)-$;

X^1 is NR^4 , S, $\text{S}(=\text{O})$, $\text{S}(=\text{O})_2$, O, CH_2 , $\text{C}(=\text{O})$, $\text{C}(=\text{CH}_2)$, $\text{CH}(\text{OH})$, $\text{CH}(\text{CH}_3)$, $\text{CH}(\text{OCH}_3)$, $\text{CH}(\text{SCH}_3)$, $\text{CH}(\text{NR}^{5a}\text{R}^{5b})$, CH_2-NR^4 or NR^4-CH_2 ;

DOCKET NO.: JANS-0026 (JAB-1499 US)

PATENT

Application No.: 10/019,380

Office Action Dated: October 29, 2003

X^2 is a direct bond, CH_2 , $C(=O)$, NR^4 , $C_{1-4}alkyl-NR^4$, $NR^4-C_{1-4}alkyl$;

u is 2 or 3;

v is 2; and

whereby each hydrogen atom in the carbocycles and the heterocycles defined in radicals (b-4), (b-5), and (b-6) may optionally be replaced by R^3 ; with the proviso that when R^3 is hydroxy or $C_{1-6}alkyloxy$, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is $C_{1-10}alkanediyl$ substituted with one or more hydroxy, $C_{1-6}alkyloxy$, aryl $C_{1-6}alkyloxy$, $C_{1-6}alkylthio$, aryl $C_{1-6}alkylthio$, $HO(-CH_2-CH_2-O)_n$ -, $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$ - or aryl $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$ -;

R^1 is a monocyclic heterocycle or aryl; said heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more substituents selected from halo, hydroxy, amino, cyano, carboxy, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, $C_{1-6}alkylthio$, $C_{1-6}alkyloxyC_{1-6}alkyl$, aryl, aryl $C_{1-6}alkyl$, aryl $C_{1-6}alkyloxy$, hydroxy $C_{1-6}alkyl$, mono- or di($C_{1-6}alkyl$)amino, mono- or di($C_{1-6}alkyl$)amino $C_{1-6}alkyl$, polyhalo $C_{1-6}alkyl$, $C_{1-6}alkylcarbonylamino$, $C_{1-6}alkyl-SO_2-NR^{5c}$ -, aryl- SO_2-NR^{5c} -, $C_{1-6}alkyloxycarbonyl$, $-C(=O)-NR^{5d}R^{5d}$, $HO(-CH_2-CH_2-O)_n$ -, halo($-CH_2-CH_2-O)_n$ -, $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$ -, aryl $C_{1-6}alkyloxy(-CH_2-CH_2-O)_n$ - and mono- or di($C_{1-6}alkyl$)amino($-CH_2-CH_2-O)_n$;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, $C_{1-6}alkylcarbonyl$, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, $C_{3-7}cycloalkyl$ substituted with $N(R^6)_2$, or $C_{1-10}alkyl$ substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, $C_{3-7}cycloalkyl$, $C_{2-5}alkanediyl$, piperidinyl, mono- or di($C_{1-6}alkyl$)amino, $C_{1-6}alkyloxycarbonylamino$, aryl and aryloxy;

R^3 is hydrogen, hydroxy, $C_{1-6}alkyl$, $C_{1-6}alkyloxy$, aryl $C_{1-6}alkyl$ or aryl $C_{1-6}alkyloxy$;

DOCKET NO.: JANS-0026 (JAB-1499 US)

PATENT

Application No.: 10/019,380

Office Action Dated: October 29, 2003

R^4 is hydrogen, C_{1-6} alkyl or aryl C_{1-6} alkyl;
 R^{5a} , R^{5b} , R^{5c} and R^{5d} each independently are hydrogen or C_{1-6} alkyl; or
 R^{5a} and R^{5b} , or R^{5c} and R^{5d} taken together form a bivalent radical of formula
 $-(CH_2)_s-$ wherein s is 4 or 5;
 R^6 is hydrogen, C_{1-4} alkyl, formyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl or
 C_{1-6} alkyloxycarbonyl;
aryl is phenyl or phenyl substituted with 1 or more-substituents selected from
halo, hydroxy, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, polyhalo C_{1-6} alkyl, and C_{1-6} alkyloxy; and
Het is pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl.

2. *(cancelled)*

3. *(previously presented)* A compound according to claim 1, wherein R^1 is phenyl optionally substituted with halo, C_{1-6} alkyl or C_{1-4} alkyloxy; or pyridyl optionally substituted with 1 or more substituents selected from aryl C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyl, aryl, mono-or di(C_{1-6} alkyl)amino, $C(=O)-NR^{5c}R^{5d}$, halo or C_{1-6} alkyl.

4. *(previously presented)* A compound according to claim 1, wherein G is C_{1-4} alkanediyl substituted with hydroxy, C_{1-6} alkyloxy, $HO(-CH_2-CH_2-O)_n-$, C_{1-6} alkyloxy $(-CH_2-CH_2-O)_n-$ or aryl C_{1-6} alkyloxy $(-CH_2-CH_2-O)_n-$.

5. *(previously presented)* A compound according to claim 1, wherein Q is a radical of formula (b-5) wherein v is 2 and Y^1 is $-NR^2-$.

6. *(previously presented)* A compound according to claim 1, wherein X^1 is NH or CH_2 .

7. *(previously presented)* A compound according to claim 1, wherein R^2 is hydrogen or C_{1-10} alkyl substituted with NHR^6 wherein R^6 is hydrogen or C_{1-6} alkyloxycarbonyl.

DOCKET NO.: JANS-0026 (JAB-1499 US)

PATENT

Application No.: 10/019,380

Office Action Dated: October 29, 2003

8. *(previously presented)* A compound according to claim 1, wherein the compound is

[(A),(S)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-1H-benzimidazol-2-amine;

[(A),(S)]-N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-4-methyl-1H-benzimidazol-2-amine trihydrochloride trihydrate;

[(A),(R)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

[(A),(S)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

[(A),(R)]-N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-2-benzimidazol-2-amine;

(±)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

[(B),(S)]N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-3-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-7-methyl-3H-imidazo[4,5-b]pyridin-2-amine;

DOCKET NO.: JANS-0026 (JAB-1499 US)
Application No.: 10/019,380
Office Action Dated: October 29, 2003

PATENT

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)(6-phenyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-4-methyl-1H-benzimidazol-2-amine monohydrate;

[(A),(R)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-1H-benzimidazol-2-amine;

a prodrug, addition salt, or stereochemically isomeric form thereof.

9. *(previously presented)* A method of treating a respiratory syncytial viral infection, comprising the step of administering a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.

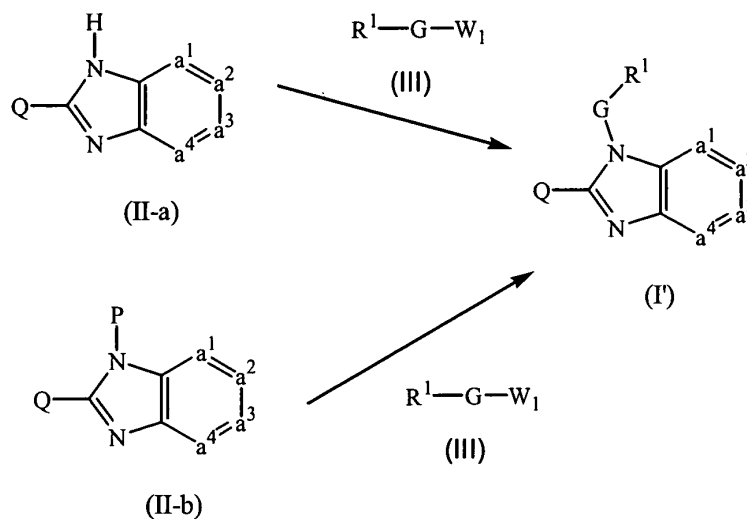
10. *(previously presented)* A pharmaceutical composition, comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.

11. *(previously presented)* A process of preparing a composition as claimed in claim 10, comprising the step of intimately mixing said carrier with said compound.

Claims 12 to 14 *(cancelled)*

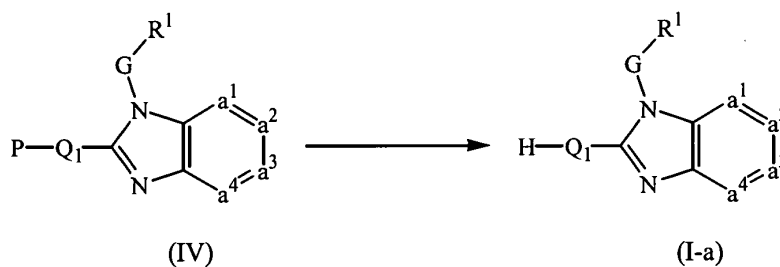
15. *(previously presented)* A process of preparing a compound as claimed in claim 1, comprising at least one step selected from the group consisting of:

- a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)



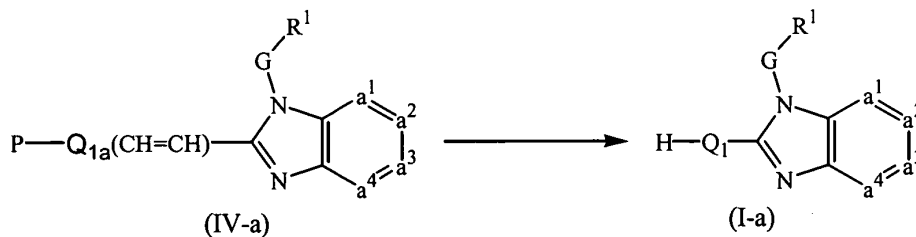
with R^1 , G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and W_1 being a leaving group, in the presence of a base and in a reaction-inert solvent;

b) deprotecting an intermediate of formula (IV)



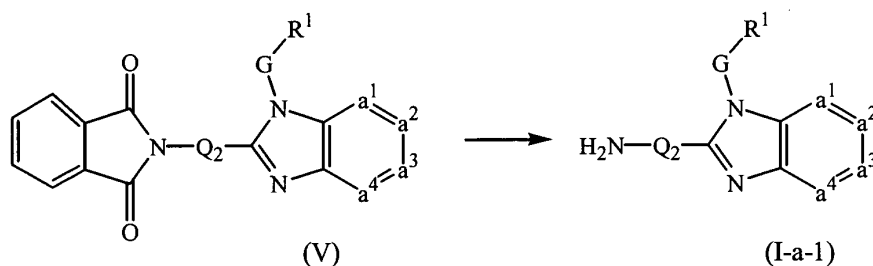
with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H- Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

c) deprotecting and reducing an intermediate of formula (IV-a)



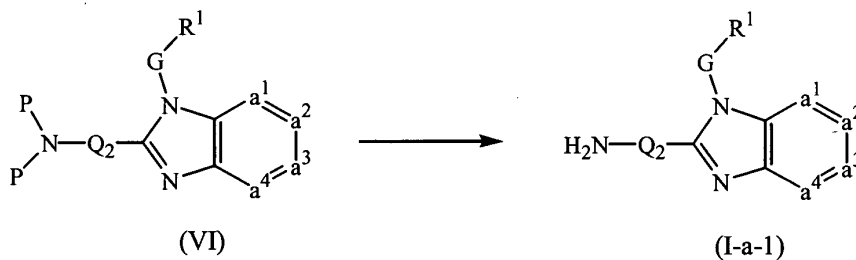
with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H-Q₁ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, Q_{1a}(CH=CH) being defined as Q₁ provided that Q₁ comprises an unsaturated bond, and P being a protective group;

- d) deprotecting an intermediate of formula (V)



with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H₂N-Q₂ being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

- e) deprotecting an intermediate of formula (VI)



with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H₂N-Q₂ being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

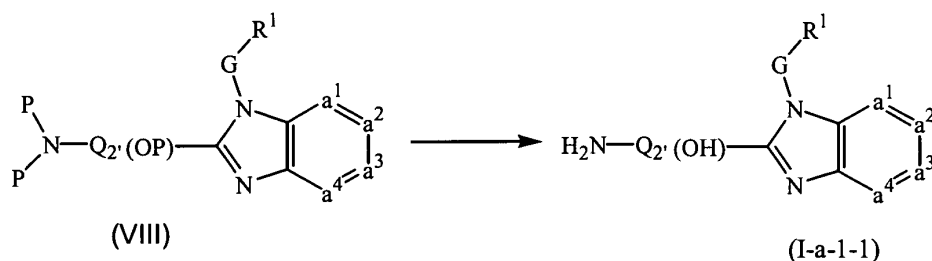
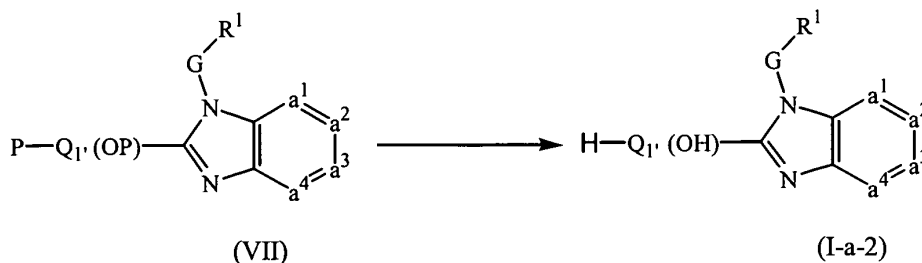
- f) deprotecting an intermediate of formula (VII) or (VIII)

DOCKET NO.: JANS-0026 (JAB-1499 US)

Application No.: 10/019,380

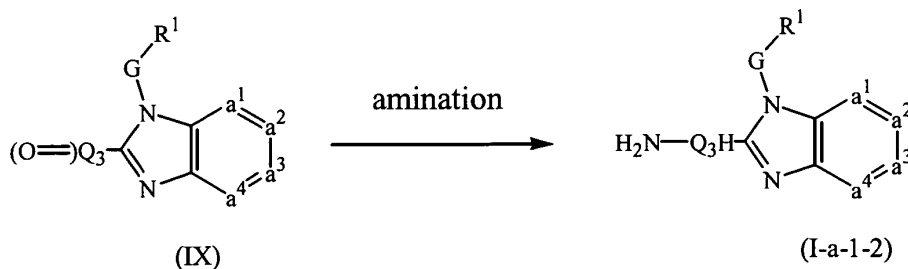
Office Action Dated: October 29, 2003

PATENT



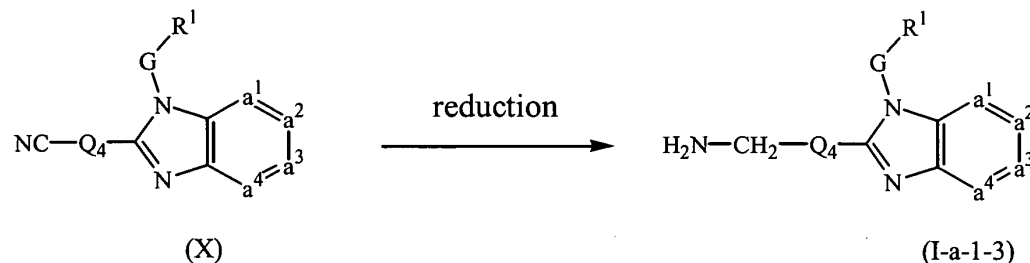
with R^1 , G , and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H-Q_1'(OH)$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, $H_2N-Q_2'(OH)$ being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

g) amination of an intermediate of formula (IX)



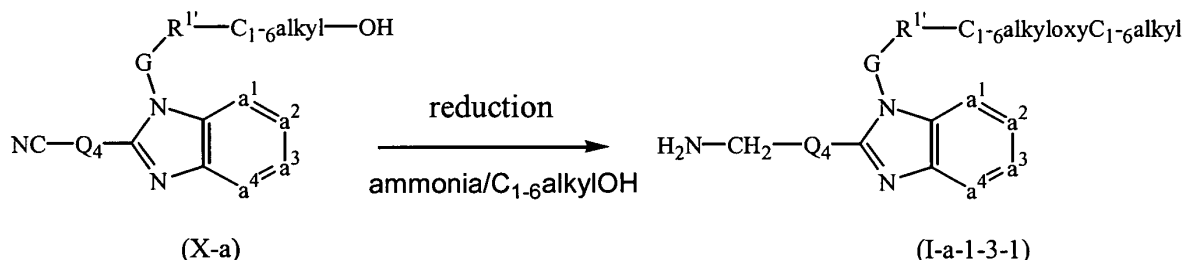
with R^1 , G , and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_3H being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6 , or R^2 and R^4 substituents contains at least one hydrogen, in the presence of an amination reagent;

h) reducing an intermediate of formula (X)



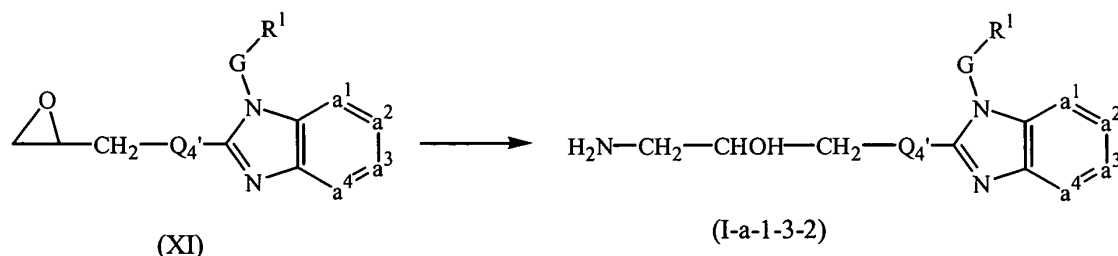
with R¹, G, and -a¹=a²-a³=a⁴- defined as in claim 1, and H₂N-CH₂-Q₄ being defined as Q according to claim 1 provided that Q comprises a -CH₂-NH₂ moiety, in the presence of a reducing agent;

i) reducing an intermediate of formula (X-a)



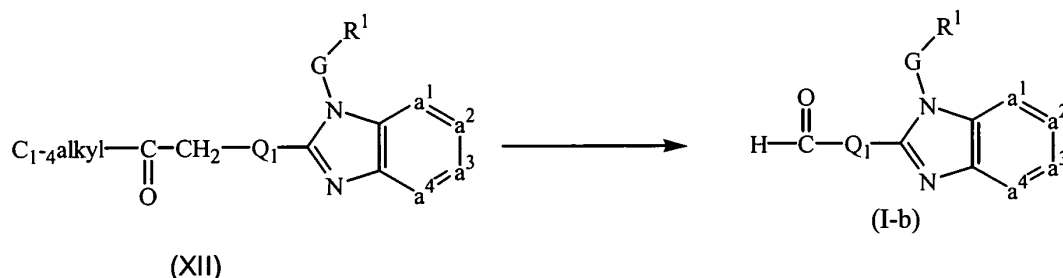
with G, and -a¹=a²-a³=a⁴- defined as in claim 1, H₂N-CH₂-Q₄ being defined as Q according to claim 1 provided that Q comprises a -CH₂-NH₂ moiety, and R^{1'} being defined as R¹ according to claim 1 provided that it comprises at least one substituent, in the presence of a reducing agent and solvent;

j) amination of an intermediate of formula (XI)



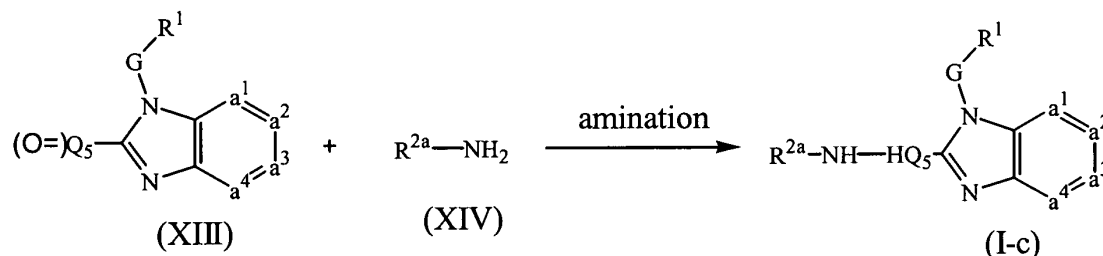
with R¹, G, and -a¹=a²-a³=a⁴- defined as in claim 1, and H₂N-CH₂-CHOH-CH₂-Q₄' being defined as Q according to claim 1 provided that Q comprises a CH₂-CHOH-CH₂-NH₂ moiety, in the presence of an amination reagent;

- k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia



with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H-C(=O)-Q_1$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is formyl;

- l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)



with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $R^{2a}-NH-HQ_5$ being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by R^{2a} , R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a reducing agent;

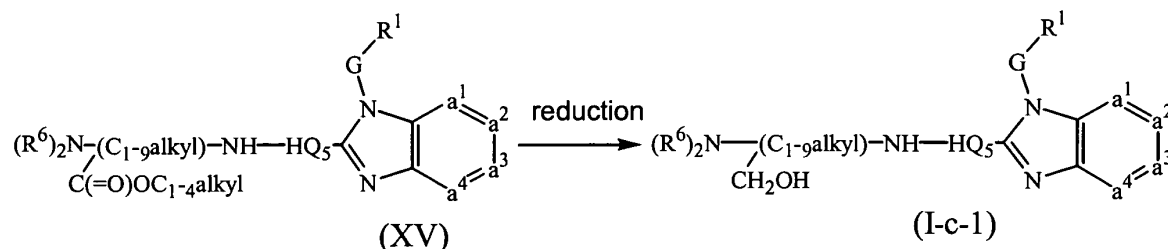
- m) reducing an intermediate of formula (XV)

DOCKET NO.: JANS-0026 (JAB-1499 US)

Application No.: 10/019,380

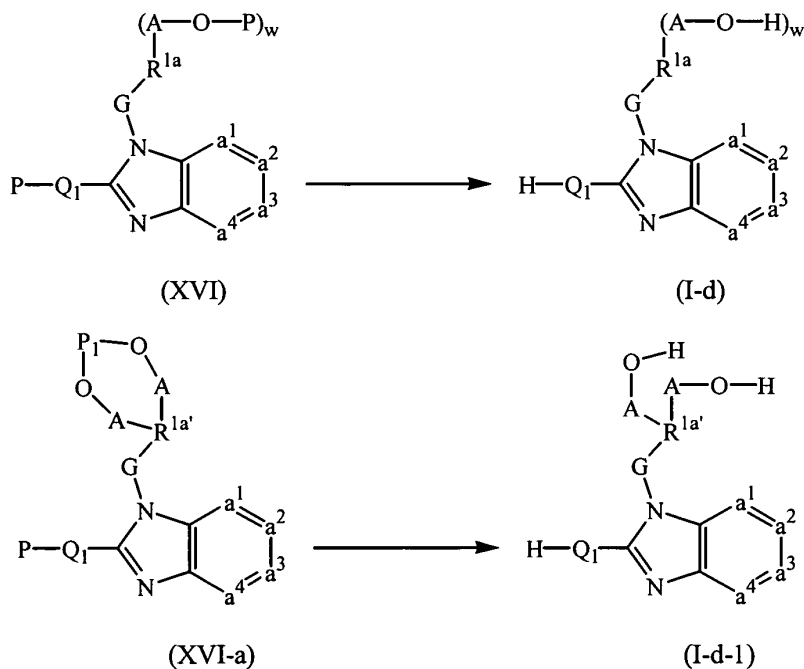
Office Action Dated: October 29, 2003

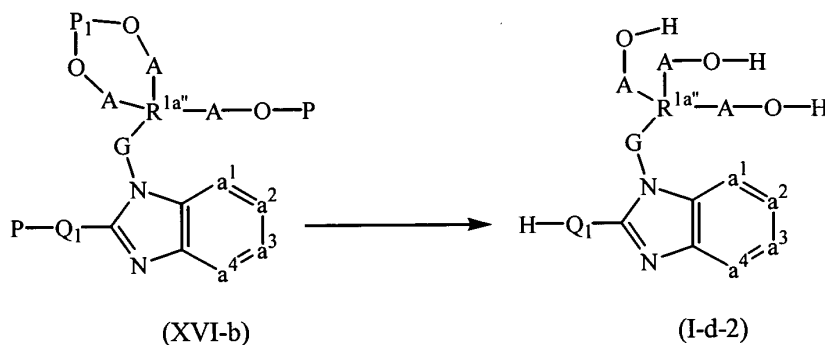
PATENT



with R^1 , G , and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(R^6)_2N-[(C_{1-9}alkyl)CH_2OH]-NH-HQ_5$ being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by $C_{1-10}alkyl$ substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a reducing agent;

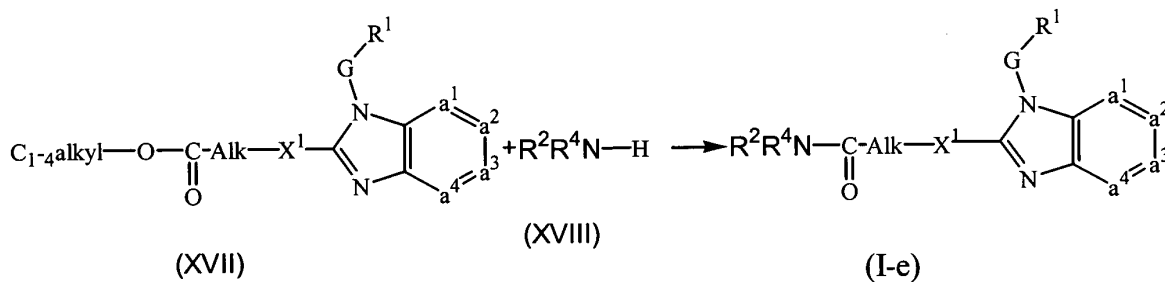
n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)





with G, and -a¹=a²-a³=a⁴- defined as in claim 1, and H-Q₁ being defined as Q according to claim 1 provided that R² or at least one R⁶ substituent is hydrogen, and R^{1a}-(A-O-H)_w, R^{1a'}-(A-O-H)₂ and R^{1a''}-(A-O-H)₃ being defined as R¹ according to claim 1 provided that R¹ is substituted with hydroxy, hydroxyC₁₋₆alkyl, or HO(-CH₂-CH₂-O)_n-, with w being an integer from 1 to 4 and P or P₁ being a protecting group, with an acid;

- o) amination of an intermediate of formula (XVII)



(XVII)

(XVIII)

(I-e)

with R¹, G, -a¹=a²-a³=a⁴-, Alk, X¹, R² and R⁴ defined as in claim 1, in the presence of an amination agent;

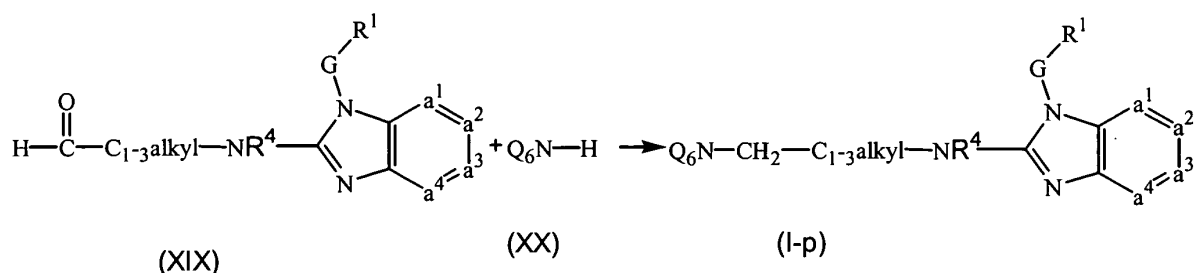
- p) amination of an intermediate of formula (XIX)

DOCKET NO.: JANS-0026 (JAB-1499 US)

PATENT

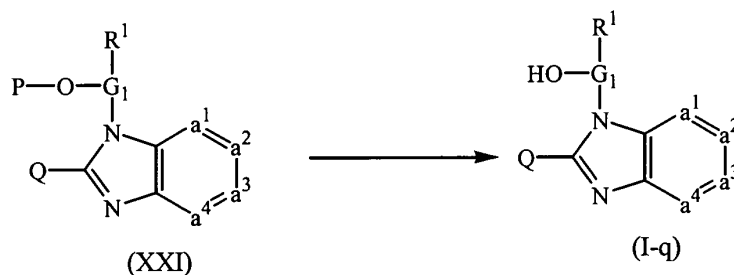
Application No.: 10/019,380

Office Action Dated: October 29, 2003



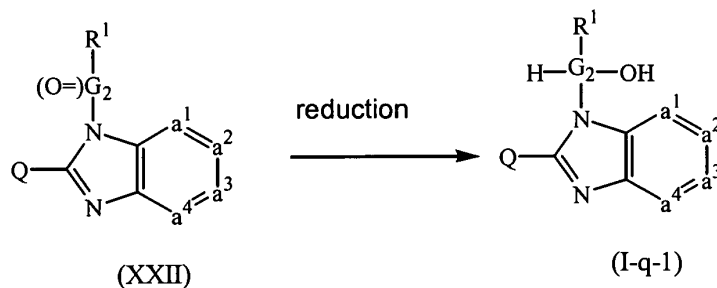
with R^1 , G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $Q_6N-CH_2-C_{1-3}alkyl-NR^4$ being defined as Q according to claim 1 provided that in the definition of Q, X^2 is $C_{2-4}alkyl-NR^4$, in the presence of an amination agent;

- q) deprotecting an intermediate of formula (XXI)



with R^1 , Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $HO-G_1$ being defined as G according to claim 1 provided that G is substituted with hydroxy or $HO-(CH_2CH_2O)_n$; and

- r) reducing an intermediate of formula (XXII)



with R^1 , Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H-G_2-OH$ being defined as G according to claim 1 provided that G is substituted with hydroxy

DOCKET NO.: JANS-0026 (JAB-1499 US)

PATENT

Application No.: 10/019,380

Office Action Dated: October 29, 2003

and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, in the presence of a reducing agent.

Claims 16 to 17 (*cancelled*)

18. (*currently amended*) The process of claim 15, further comprising the step of converting said compound of formula (I'), or a stereochemically isomeric form ~~forms, metal complexes, quaternary amines or N-oxide forms~~ thereof, into a therapeutically active non-toxic acid addition salt by treatment with an acid.

19. (*currently amended*) The process of claim 15, further comprising the step of converting said compound of formula (I'), or a stereochemically isomeric form ~~forms, metal complexes, quaternary amines or N-oxide forms~~ thereof, into a therapeutically active non-toxic base addition salt by treatment with alkali.

20. (*previously presented*) The process of claim 15, further comprising the step of converting the acid addition salt form of compound of formula (I') or stereochemically isomeric forms, thereof, into the free base by treatment with alkali.

21. (*previously presented*) The process of claim 15, further comprising the step of converting the base addition salt form of compound of formula (I') or stereochemically isomeric forms, thereof, into the free acid by treatment with acid.

22. (*currently amended*) The process of claim 15, further comprising the step of converting said compound of formula (I') or stereochemically isomeric form, into a different form of said compound of formula (I'), or a stereochemically isomeric form, ~~metal complex, quaternary amine or N-oxide form~~ thereof.